REMARKS

Applicants submit this response to the Office Action dated May 25, 2004. Claims 12-18 and 22 are pending as of the date of the Office Action, and claims 1-11, 12-14, 19-21, 22 and 23-59 have been cancelled. The remarks below are in numbered paragraphs to correspond to the Office Action.

1. Applicants confirm the status of the claims, and claims 12-18 and 22 were elected in response to a restriction requirement.

2. Applicants acknowledge entry of the preliminary amendment, and the current pending status of claims 12-18 and 22.

3. In response to the notice regarding sequence compliance, applicants have amended the specification to indicate the sequence identifiers.

4. Applicants acknowledge receipt of the signed copy of form PTO-1449.

5. Applicants acknowledge that the drawings filed on May 21, 2002 are accepted.

6. In response to the objection to the disclosure, the brief description of the drawings has been amended to refer to the separate panels of the drawings. This amendment has been made for Figures 7-9. Regarding Figures 4 and 5, unlike Figures 7-9 these figures do not show separate panels (A, B, etc.). Figures 4 and 5 show different sequences but the figure legends currently correspond to the SEQ ID NO: designations in the drawings of Figures 4 and 5.

7. In response to the objection to the Abstract, the Abstract has been revised and a correction is submitted herein, to omit the typed text at the end of the page.

8-9. *Rejection under 35 U.S.C. § 112, first paragraph.* Claims 12-16 and 22 are rejected under 35 U.S.C. § 112, first paragraph. Claims 12-14 and 22 have been cancelled without prejudice to the subject matter and without acquiescing to the ground of rejection. The Examiner states that the specification is enabling for an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:4 and its epitope-bearing portion comprising SEQ ID NO:7 or 8, but that the specification does not provide enablement for a genus of polypeptides comprising a fragment of SEQ ID NO:4, a variant homologue of SEQ ID NO:4 or its fragment, or an epitope-bearing portion of SEQ ID NO:4. The Examiner cited *Ex parte Forman*, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986) and *In re Wands*, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988). Applicants respectfully traverse this rejection, and address the specific factors below.

A specification is presumed to be enabling and the U.S. Patent and Trademark Office (PTO) has the burden of establishing a *prima facie* case of lack of enablement. See, In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976); In re Marzocchi, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971). To make a *prima facie* case of lack of enablement, the PTO must come forward with reasons, supported by the record as a whole, showing why the specification fails to enable one of ordinary skill in the art to make and use the claimed invention. In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). The mere fact that some experimentation is necessary does not negate enablement as long as undue experimentation is not required. See M.P.E.P. § 608.01(p).

The burden is on the PTO to establish that experimentation would be undue, Angstadt, 190 U.S.P.Q. at 219, taking into consideration the eight factors that are to be considered in determining whether a disclosure requires undue experimentation. In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Applicants submit that the amount of experimentation which may be required to practice the present invention does not rise to the level of being undue experimentation, as defined by the Court in Wands.

An important aspect of the Court's decision in Wands is its finding that the nature of the technology pertinent to the Wands invention (monoclonal antibody production) permitted a broad definition of the term "experiment." The Court found that an "experiment" in the monoclonal antibody art consisted of the entire attempt to make a monoclonal antibody against a particular antigen. As described by the Court, the process entailed, "immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics." 8 U.S.P.Q.2d at 1407. Thus, Wands supports the conclusion that in, a complex field such as monoclonal antibody production, the entire attempt to achieve the desired result, from beginning to end, constitutes one experiment.

According to the Court, repetition of this whole experiment more than once does not constitute undue experimentation. As the Court indicated, practitioners in the art would be prepared to screen negative hybridomas in order to find a hybridoma making the desired antibody. 8 U.S.P.Q.2d at 1406. Thus, the fact that some aspects of the experiment as a whole will yield negative results does not mandate a finding that the amount of experimentation to achieve a positive result is undue.

Like the production of monoclonal antibodies, the identification or production of a FGF-21 polypeptide having the limitations of the present claims may require some experimentation, but if viewed in the light of Wands, this experimentation, and the possibility of encountering negative results along the path to the positive results, is not undue. Furthermore, the present applicants provide extensive guidance to allow one of ordinary skill in the art to obtain a polypeptide that is within the scope of the claims.

Applicants submit that one of ordinary skill in the art can construct an antibody as described in the specification at page 26, line 15 to page 27, line 22, and at page 36, lines 5-14. A candidate polypeptide that might fall within the scope of the claims would be tested for (a) specific binding to an anti-huBUB3 antibody, and (b) homology with the amino acid sequence of SEQ ID NO:2 as specified in the claims. If the results of these tests were positive, the polypeptide sequence would fall within the scope of the claims. Such tests would not constitute "undue" experimentation within the scope of Wands, as discussed in detail below.

The inventors have identified and sequenced a human protein referred to as FGF-21.

Applying this information to the eight Wands factors, one of skill in the art would conclude that undue experimentation would not be required to practice the claimed invention.

1. *Quantity of experimentation necessary.* To determine if a polypeptide falls within the scope of the claims, the only experimentation required is the performance of known antibody binding and sequencing procedures. These procedures are routine and would not have to be done repeatedly before a definitive result was obtained. Because the inventors and the art provide means for the objective measurement of a polypeptide falling within the claim scope, this factor is met, for example, by the ability of the polypeptide to bind to an anti-FGF-21 antibody. This is described in the specification as noted above.

The Wands court found that practitioners in the art are prepared to screen negative hybridomas to find one that made the desired antibody. (USPQ2d at 1406.) The court further stated that an "experiment" was not simply the screening of a simple hybridoma, but instead was the entire attempt to make a monoclonal antibody against a particular antigen. This process included immunizing animals, fusing lymphocytes from the immunized animals to make hybridomas, cloning the hybridomas, and screen the antibodies produced by the hybridomas. (USPQ2d at 1406).

By analogy, a single experiment in the present art could include obtaining or constructing a polypeptide, contacting it with anti-FGF-21 antibody, and determining the amino acid sequence of the polypeptide. Encountering negative results would not mean that undue experimentation is involved, according to Wands.

2. *Amount of direction or guidance provided.* The specification provides clear directions for performing the experimentation, and cites to published scientific articles for details not mentioned in the specification. Similarly, the Wands court found that the starting material was available to the public (as is the material used in the present application) and the patent at issue in Wands provided a detailed description of the methods, which included use of a commercially available kit. (8 USPQ 2d at 1404, 1405).

3. *Presence of absence of working examples.* The specification describes the human FGF-21 protein of SEQ ID NO:4, and one of skill in the art is familiar with methods of producing and testing antibodies, for example as described at page 26, line 15 to page 27, line 22.

4. *Nature of the invention.* The invention relates to human polypeptides. Methods of synthesizing, isolating, mutating, manipulating, transfecting, and expressing polypeptides are the basis for the biotechnology industry. The nature of the invention is such that it is well-known to those of ordinary skill in the art. The court in Wands stated that the nature of monoclonal antibody technology is that it involves screening, including screening of negative samples (in that case, hybridomas). The number of potentially negative samples was not viewed as a determining factor in reaching a finding of undue experimentation (8 USPQ 2d at 1406-1407).

5. *The state of the prior art.* The prior act provides the methods and materials needed to apply the methods of factor (4) above to this group of polypeptides, specifically FGF-21 polypeptides. The Wands court found that "all the methods needed to practice the invention were well-known." (8 USPQ 2d at 1406). Similarly, the methods of constructing or expressing protein, measuring protein binding to antibodies, and determining amino acid sequences are well known.

6. *The relative skill of those in the art.* Those of skill in this art are highly skilled and would be competent at designing and performing, or directing the performance of, the procedures of factors (4) and (5) above. The Wands court found that the level of skill in the monoclonal antibody art was high at the time the application was filed, but, importantly, the court found that development of skill in performing specific experiments relevant to the art did not preclude enablement. Specifically, the court stated that initial failures occurred as the inventors learned to fuse cells, and "[o]nce they became skilled in the art, they invariably obtained numerous hybridomas ..." that met the claim limitations. (8 USPQ 2d at 1406). By analogy, it would not defeat enablement for one of skill in the act of protein chemistry and sequencing to learn and become proficient in techniques for practicing the present invention.

7. *The predictability or unpredictability of the art.* One of skill, being acquainted with the methods described in the application, would predict that when a polypeptide specifically binds to an antibody raised against FGF-21, it will share amino acid sequence characteristics of SEQ ID NO:4, and this can be routinely confirmed by amino acid sequence determination and alignment with SEQ ID NO:4.

In Wands, the Court noted that the cell fusion technique was well known to those of ordinary skill in the art, and that there was no indication that the fusion step should be more difficult or unreliable for the antigen in question (HBsAg) than for other antigens. The Examiner has provided no evidence that the steps of preparing and sequencing polypeptides would be "more difficult or unreliable" (8 USPQ2d at 1406) than for SEQ ID NO:4.

8. *The breadth of the claims.* Using materials and methods routinely available at the time of filing, one of skill can routinely identify or construct any polypeptide molecule meeting the limitations of the claims, and test it for anti-FGF-21antibody binding as described for the previous factors.

In view of the foregoing remarks, applicants submit that the Examiner has not met her burden of making a *prima facie* showing that undue experimentation is required in order to practice the invention as claimed. Reconsideration and withdrawal of this rejection are respectfully requested.

10. *Rejection under 35 U.S.C. § 112, first paragraph.* Claims 12-16 and 22 are rejected under 35 U.S.C. § 112, first paragraph. The Examiner states that these claims contain subject matter that was not described in the specification in such a manner as to convey that the inventors had possession of the claimed invention at the time of filing. Claims 12-14 and 22 have been cancelled. Applicants respectfully traverse this rejection for the reasons discussed below.

One intent of the written description requirement is to prevent applicants from claiming priority to earlier applications if the current application discloses new matter not present in the earlier applications (Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991)). Further, In re Kaslow affirms that "the test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at the time of the later claimed subject matter, *rather than the presence or absence of literal support in the specification for the claim language*." (707 F.2d 1366, 1375 (Fed. Cir. 1983) emphasis added). Applicants respectfully submit that the Examiner has misapplied the written description requirement in this case. While the current application is a divisional application of an earlier application, the claimed subject matter is fully supported by the specification of the current application, and the Examiner has provided no support for a position that the applicants must demonstrate literal support in the specification for sequence variants of SEQ ID NO:4 and additional epitopes of SEQ ID NO:4. Reconsideration and withdrawal of this rejection are respectfully requested.

11-12. *Rejection under 35 U.S.C. § 102(e).* Claims 12-14 and 22 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Agarwal *et al.* (US 2001/0012628A1, published August 9, 2001, earliest priority date November 5, 1999). Without acquiescing to the grounds of rejection, applicants have cancelled claims 12-14 and 22 without prejudice to pursuing this subject matter in a continuation or divisional application. Withdrawal of this rejection is respectfully requested.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

If questions remain regarding this application, the Examiner is invited to contact the undersigned at (206) 628-7650.

Respectfully submitted,
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